



## CDEC FINAL RECOMMENDATION

### OCRIPLASMIN

(Jetrea — Alcon Canada Inc.)

**Indication: Symptomatic Vitreomacular Adhesion**

#### **Recommendation:**

The Canadian Drug Expert Committee (CDEC) recommends that ocriplasmin be listed for the treatment of symptomatic vitreomacular adhesion (VMA) if the following clinical criteria and conditions are met:

#### **Clinical Criteria:**

- Diagnosis of VMA should be confirmed through optical coherence tomography.
- Patient does not have any of the following: large diameter macular holes (> 400 µm), high myopia (> 8 dioptre spherical correction or axial length > 28 mm), aphakia, history of retinal detachment, lens zonule instability, recent ocular surgery or intraocular injection (including laser therapy), proliferative diabetic retinopathy, ischemic retinopathies, retinal vein occlusions, exudative age-related macular degeneration, or vitreous hemorrhage.

#### **Conditions:**

- Ocriplasmin should be administered by a retinal specialist.
- Treatment with ocriplasmin should be limited to a single injection per eye.
- Reduced price to improve the cost-effectiveness of ocriplasmin to an acceptable level.

#### **Reasons for the Recommendation:**

1. Ocriplasmin was shown to be superior to placebo for resolution of VMA and total posterior vitreous detachment in two double-blind randomized controlled trials (RCTs) (TG-MV-006 and TG-MV-007).
2. Patients with a range of common ocular conditions were excluded from the clinical trials; therefore, there is uncertainty regarding the safety and efficacy of treatment with ocriplasmin in these patient populations. The product monograph states that treatment with ocriplasmin is not recommended in these patients.
3. At the submitted price of \$3,950 per 0.125 mg dose, the Common Drug Review (CDR) estimated that the incremental cost per quality-adjusted life-year (QALY) for ocriplasmin ranges from \$55,544 to \$124,621 depending on the assumptions used in the model.

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### **Background:**

Ocriplasmin is indicated for the treatment of symptomatic VMA. The recommended dose is a single 125 mcg intravitreal injection. Repeated administration of ocriplasmin in the same eye is not recommended. If treatment of the contralateral eye is required, this should not be performed within seven days of the injection into the first eye so the post-injection course and potential for decreased vision in the injected eye can be adequately monitored.

### **Summary of CDEC Considerations**

CDEC considered the following information prepared by CDR: a systematic review of RCTs of ocriplasmin, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

### **Patient Input Information**

The following is a summary of information provided by two patient groups that responded to the CDR call for patient input:

- VMA can lead to macular holes and serious vision loss. Vision loss can result in a loss of independence, employment and income, and ability to drive. This leads to hardship on family, social isolation, depression, and falls or other injuries.
- As ocriplasmin is a single injection rather than a surgical procedure, patients expect the treatment will result in a reduced waiting time before they are treated, which will reduce reliance on caregivers and the risk of injuries caused by impaired vision. In addition, they expect ocriplasmin to result in fewer hospitalizations, fewer doctor visits, and the avoidance of surgery.
- The requirement that patients lay face down for at least a week after a surgical treatment (e.g., vitrectomy) is the primary reason many patients would much prefer an effective non-surgical treatment.

### **Clinical Trials**

The systematic review included three multi-centre, parallel group, double-mask, placebo and sham controlled RCTs. TG-MV-006 (N = 326) and TG-MV-007 (N = 326) were identically designed phase 3 studies that evaluated the safety and efficacy of a single 125 mcg dose injection of ocriplasmin compared with placebo injection for the treatment of symptomatic VMA. TG-MV-004 (N = 60) was a phase II study that evaluated the safety and preliminary efficacy of ocriplasmin 75 mcg, 125 mcg, and 175 mcg single doses and repeated doses of ocriplasmin 125 mcg (up to two additional open-label injections) compared with a sham injection. Given the numerous limitations of TG-MV-004 pertaining to this report, data from this study were not presented nor discussed. Thus, the two phase 3 studies, TG-MV-006 and TG-MV-007, served as the primary source for efficacy and safety in this report.

### **Outcomes**

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Resolution of VMA at day 28, three months, and six months.
- Change from baseline in health-related quality of life — measured using the National Eye Institute Visual Function Questionnaire (VFQ-25) at six months.
- Total posterior vitreous detachment (PVD) at day 28.
- Non-surgical closure of full thickness macular hole (FTMH) at day 28.

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- The proportion of patients receiving vitrectomy (avoidance of vitrectomy).
- Change from baseline in best corrected visual acuity (BCVA).

The primary outcome in studies TG-MV-006 and TG-MV-007 was proportion of patients with VMA resolution, determined by optical coherence tomography at day 28.

### Results

#### Efficacy

- Ocriplasmin demonstrated statistical superiority to placebo for resolution of VMA at day 28, three months, and six months. The risk difference for achieving resolution of VMA with ocriplasmin versus placebo was reported as follows:
  - Day 28: 14.8% (95% confidence interval [CI], 6.0% to 23.5%) in TG-MV-006 and 19.1% (95% CI, 11.6% to 26.7%) in TG-MV-007.
  - Three months: 11.5% (95% CI, 2.6% to 20.5%) in TG-MV-006 and 16.7% (95% CI, 8.5% to 24.9%) in TG-MV-007.
  - Six months: 13.4% (95% CI, 4.5% to 22.2%) in TG-MV-006 and 14.2% (95% CI, 5.1% to 23.2%) in TG-MV-007.
- Statistically significant results were only observed in TG-MV-007 for the VFQ-25 composite score. The ocriplasmin group had a greater mean standard deviation (SD) change from baseline in composite score 3.3 (11.97) compared with the placebo group -0.1 (10.29) ( $P = 0.013$ ) at six months.
- A larger proportion of patients in the ocriplasmin groups achieved total PVD at day 28 in both studies with a between-group difference of 9.9% (95% CI, 3.1% to 16.7%) in TG-MV-006 and 10.6% (95% CI, 6.8% to 14.5%) in TG-MV-007.
- At day 28, the ocriplasmin groups were statistically superior to placebo groups for the achievement of non-surgical closure of FTMH with a between-group difference of 31.4% (95% CI, 14.1% to 48.6%) in TG-MV-006 and 30.1% (95% CI, 11.6% to 48.6%) in TG-MV-007. At six months, similar results were seen, but statistical significance was reached only in TG-MV-006 with a between-group difference of 30.0% (95% CI, 11.9% to 48.0%).
- In both studies, the proportion of patients receiving vitrectomy was greater in the placebo groups compared with the ocriplasmin groups at day 28 and six months, though differences were not statistically significant. The actual effect of ocriplasmin in avoiding vitrectomy is uncertain due to potential patient and physician selection bias as the decision to perform vitrectomy was at the discretion of patients and investigators.
- For change from baseline in BCVA, the proportion of patients who had an improvement of 15 letters or more at six months was greater in the ocriplasmin group compared with placebo in TG-MV-007 with a between-group difference of 8.1% (95% CI, 2.3% to 13.9%); however, the between-group difference was not statistically significant in TG-MV-006.
- In both studies, no statistically significant differences were observed for improvement and worsening of 15 letters or more at day 28, worsening of 15 letters or more at six months, improvement of 30 letters or more and worsening of 30 letters or more at day 28 and six months.

#### Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event was greater in the ocriplasmin groups (42.3% and 38.0%) compared with the placebo groups (19.8% and

23.5%) in TG-MV-006 and TG-MV-007 respectively. The most commonly reported adverse events were vitreous floaters, photopsia, visual impairment, and eye pain.

- The proportion of patients who experienced at least one serious adverse event was similar between ocriplasmin and placebo in TG-MV-006 (14.5% versus 12.3% respectively) and in TG-MV-007 (13.5% versus 13.6% respectively).
- Withdrawals due to adverse events were reported for 0.9% and 0.8% of patients in the ocriplasmin groups and 1.9% and 0% of patients in the placebo groups in TG-MV-006 and TG-MV-007 respectively.

### **Cost and Cost-Effectiveness**

The manufacturer conducted a cost-utility analysis comparing ocriplasmin with watchful waiting (medical management), with the option of vitrectomy in either strategy, using data from TG-MV-006 and TG-MV-007. The analysis was conducted over the patient's lifetime (up to 37.5 years), using the Canadian public-payer perspective. The economic submission is based on a six-month decision tree and a long-term Markov model.

In the monthly cycle decision tree, a patient with vitreomacular traction (VMT) can experience: non-surgical VMT resolution at day 28; a vitrectomy for VMT depending on the patient's visual acuity (VA); and, non-surgical resolution or macular hole (MH) at six months. All patients (VMT and MH) are allocated to the following health states in the Markov model: resolved; VMT unresolved without MH; VMT unresolved with MH; VMT resolved with MH (no vitrectomy); VMT resolved with MH (1 vitrectomy); VMT resolved with MH (2 vitrectomies); and death. Within each Markov cycle, patients can transition between disease health states and between VA health states (no change, improve, or worsen). Patients continue to experience the following events: VMT resolution only, MH closure only, VMT resolution and MH closure, and VMT progressing to MH. Each of the health states is associated with a different distribution of VA categories. For patients achieving resolution of VMT, the VA of these patients was assumed to follow the age-matched general Finnish population's long-term VA decline. VA for patients with persistent VMT (i.e., all disease states except "resolved") was assumed to decline gradually, but at a faster rate than the general population. Adverse events, including cataract after vitrectomy, retinal tear, retinal detachment, elevated intraocular pressure and vitreous hemorrhage, were also considered in the model based on rates observed from the RCTs and data on file. The majority of the transition probabilities in the decision tree (first six months) were taken from the RCTs, except the probability of a second vitrectomy for MH and its success rate, which were based on clinical opinion. Transition probabilities in the Markov model were estimated using a regression model based on the trial data, expert opinion, and published literature. Beyond six months the probability of spontaneous resolution of VMA was assumed to be 0%. Utilities were obtained from the published literature and assumptions. The manufacturer reported an incremental cost per QALY for ocriplasmin compared with watchful waiting of \$40,124 using the health-payer perspective.

CDR noted the following limitations:

- Generalizability and inclusion of non-health-care payer costs
  - Resource utilization associated with visual impairment was obtained from a costing study in wet age-related macular degeneration patients; the generalizability to this population was not discussed.
  - The blindness health state included lost productivity and indirect costs, the incremental cost-utility ratio (ICUR) increases to \$43,657 per QALY when indirect costs were excluded.

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- Bilateral disease
  - The manufacturer did not consider the cost of treating bilateral disease, which occurred in 19.9% of trial participants. According to the clinical expert consulted by CDR during this review, both affected eyes are likely to be treated in usual clinical practice.
- Short duration of clinical trial and assumption of long-term relative efficacy
  - The RCTs were six months in duration and assessed VMA resolution (as opposed to VA); it has not been established that long-term differences in the clinically important outcome of VA (the major factor driving quality of life and disease costs) will occur. If the treatment effect attenuates, the cost-effectiveness ratio will increase. In the manufacturer's sensitivity analysis, shortening the time horizon to two years, the incremental QALYs decreased from 0.069 to 0.024 and the cost per QALY increased to \$147,816, highlighting that a majority of the incremental benefit accrued in the model is beyond the time frame of the RCTs.
- Uncertainty on VMA status and long-term effects on VA
  - An important assumption in the manufacturer's model is that the greater VMA resolution achieved with ocriplasmin will ultimately result in improved VA (the major determinant of efficacy in the model), which was not consistently observed for ocriplasmin in the RCTs.
  - The model is limited by insufficient data to accurately estimate the long-term VA outcomes in patients with unresolved and resolved VMA.
- Uncertainty on long-term spontaneous resolution probability
  - The probability of spontaneous resolution of the VMA rate from six months to two years was set at 0%, but observational data cited by the manufacturer quoted probabilities of 2.2% and 16.5%. Using these values attenuates relative efficacy of ocriplasmin and leads to a greater ICUR for ocriplasmin.

In the base case from the CDR re-analysis, where non-health care costs were excluded and costs of ocriplasmin for bilateral disease were included, the ICUR is \$55,544 per QALY. In one-way sensitivity analyses exploring long-term efficacy, the following was found:

- assumption of no mortality benefit with ocriplasmin: ICUR \$65,957 per QALY
- assumption of the same VA trajectory beyond six months for those with and without VMA resolution: ICUR \$94,766 per QALY
- literature cited probabilities of long-term spontaneous VMA resolution of 2.2% and 16.5%: \$63,264 and \$124,621 per QALY respectively.

The cost of ocriplasmin is \$3,950 per 0.125 mg dose.

### Other Discussion Points:

CDEC noted the following:

- The intravitreal placebo injection may have resulted in complete PVD in some patients, resulting in a greater rate of spontaneous resolution than would be expected in untreated patients with VMA.

### Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- There is limited evidence regarding the long-term efficacy (e.g., vision) and safety of ocriplasmin.

- There are no head-to-head trials comparing ocriplasmin with watchful waiting or vitrectomy, the current treatments used in Canada for VMA.
- Evidence is required to address the patient populations with relevant ocular conditions who were excluded from the TG-MV-006 and TG-MV-007 clinical trials and for whom treatment with ocriplasmin is currently not recommended.

### **CDEC Members:**

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani

### **November 20, 2013 Meeting**

#### **Regrets:**

One CDEC member could not attend the meeting.

#### **Conflicts of Interest:**

None

### **About This Document:**

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